**Vitamin K: Friend or Foe in Patients on Warfarin Therapy**

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**Objectives**

- Review warfarin therapy
- Discuss the use of vitamin K supplementation in anticoagulation
- Review the literature supporting vitamin K supplementation in anticoagulation
- Identify patients who may benefit from daily vitamin K supplementation

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**Warfarin**

- **Mechanism of action**
  - Prevents regeneration of vitamin K1 epoxide by inhibiting Vitamin K Reductase (VKR) and Vitamin K Epoxide Reductase (VKOR)
  - Inhibits production of clotting factors VII, IX, X, and II
  - Inhibits production of protein C and S

**Indications**

- Deep venous thrombosis and pulmonary embolism
- Atrial fibrillation
- Valvular heart disease
- Prosthetic valve
- Antiphospholipid antibody syndrome
- Prevention of recurrent myocardial infarction

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**Barriers to successful warfarin therapy**

- **Lifestyle**
  - Follow up
  - Adherence
  - Smoking
  - Alcohol
  - Physical activity
- **Diet**
- **Drug interactions**
- **Narrow therapeutic window**
- **Genetic factors**
- **Risk of bleeding**
**Drug Interactions**

**Increase INR**
- Anti-infectives
  - Fluoroquinolones
  - Metronidazole
  - Sulfonamides
  - Macrolides
  - Azole antifungals
- Proton Pump Inhibitors
  - Omeprazole
- H2 Blockers
  - Cimetidine
  - Ranitidine
- Antiarrhythmics
  - Amiodarone
- Lipid Lowering Agents
- Antidepressants
- Anti-inflammatory
  - Corticosteroids
  - NSAIDS/Aspirin
- Thyroid Medication
- Chemotherapy
- Antiepileptics
- Vitamins E and A

**Decrease INR**
- Aluminum hydroxide
- Antithyroid
- Azathioprine
- Barbituates
- Bosentan
- Carbamazepine
- Cholestyramine
- Estrogens
- Haloperidol
- Nafcillin
- Phenytoin
- Rifampin
- Sulcralfate
- Spironolactone
+ Vitamin K

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**Vitamin K (phytonidione)**
- Vitamin K is an essential coenzyme in the production of clotting factors
  - Vitamin K is carboxylated by Vitamin K Reductase (VKR) and Vitamin K Epoxide Reductase (VKOR)
- Vitamin K necessary for proper bone metabolism and vascular repair

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**Vitamin K (phytonidione)**
- Indications
  - Hypoprothombinemia secondary to drugs
  - Vitamin K deficiency secondary to warfarin
  - Hemorrhage in newborns
- Routes
  - Orally (recommended)
  - Subcutaneous
  - Intravenous
  - Intramuscular

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**Vitamin K (phytonidione)**
- Obtained through diet
  - Recommended daily nutritional allowance is 90mcg in women and 120mcg in men
  - High yield in certain green leafy vegetables, teas, and fruits
  - Patients on warfarin should consistently consume foods that contain amounts of vitamin K
- Intestinal bacteria

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**INR**

- **Therapeutic**
- **Subtherapeutic**
- **Supratherapeutic**


Pazirandeh S. Overview of vitamin K. In: UpToDate, Lipman TO (Ed), 2008.

**CHEST GUIDELINES**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Vitamin K dose</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious bleeding/eemergency</td>
<td>10mg IV infusion, additional supplement as needed</td>
<td>1C</td>
</tr>
<tr>
<td>Variable INR, long term therapy</td>
<td>100-200mcg po daily</td>
<td>2B</td>
</tr>
</tbody>
</table>

**Why supplement**

- Patients with unstable INR consistently have low vitamin K
- Vitamin K is quickly metabolized by the liver
  - Warfarin increases vitamin K metabolism
- Increasing vitamin K body stores may replace daily intake and stabilize highly fluctuation INR

**Ford et al.**

- A 17 week prospective, open label, crossover study
  - Week 1-9 warfarin alone
  - Week 9-17 initiated vitamin K 500mcg po daily (dietary supplement)
- Results: 9 patients completed the study
  - 5 patients showed a decrease in SD of INR during vitamin K treatment

**CHEST GUIDELINES**

<table>
<thead>
<tr>
<th>INR</th>
<th>Vitamin K dose</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-9 with ↑ risk of bleeding</td>
<td>1-2.5mg po x 1 dose, then 1mg po next 24 hrs</td>
<td>2A</td>
</tr>
<tr>
<td>5-9 need for urgent surgery</td>
<td>2.5-5mg po x 1 dose</td>
<td>2C</td>
</tr>
<tr>
<td>&gt;9 with no bleeding</td>
<td>5mg po x 1 dose</td>
<td>1B</td>
</tr>
</tbody>
</table>
Reese et al.

- A retrospective analysis of 8 patients
  - Dietary supplementation with vitamin K 100mcg po daily, in patients with variable INR
  - Variable INR defined as 3 warfarin dose changes or 3 INR levels outside therapeutic window in last 6 months
- Results: Number of INR readings within targeted range increased from 32% to 57%


Sconce et al.

- A randomized, double blind, prospective, placebo-controlled study followed 70 patients with atrial fibrillation
  - Variable INR defined as 3 warfarin dose changes or 3 INR levels outside therapeutic window in last 6 months
  - 35 patients were given warfarin (placebo group)
  - 35 patients were given warfarin and daily vitamin K 150mcg oral solution


<table>
<thead>
<tr>
<th></th>
<th>Improved INR</th>
<th>Change in SD of INR</th>
<th>Change in time in range (%)</th>
<th>Dose changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group</td>
<td>24/33</td>
<td>-0.24</td>
<td>15</td>
<td>-2</td>
</tr>
<tr>
<td>Treatment group</td>
<td>33/35</td>
<td>-0.11</td>
<td>28</td>
<td>-1</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>


Conclusion

- Consider daily vitamin K in patients with 3 warfarin dose changes or 3 INR levels outside therapeutic window within the last 6 months
- Other known causes of unstable INR should be ruled out prior to vitamin K use
- Supplementation of warfarin therapy with vitamin K 160-200mcg po daily, may be beneficial in stabilizing INR in highly motivated patients
- Vitamin K supplementation requires increasing the warfarin dose and close monitoring
- Dietary supplements of vitamin K are available in 100mcg doses

Questions

1. Vitamin K supplementation works to stabilize INRs by improving the mechanism of action of warfarin.
2. Vitamin K supplementation has been proven to stabilize highly fluctuating INRs.
3. Calcium supplements containing vitamin K should be recommended in all patients highly fluctuating INRs.